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| --- | --- | --- |
| Patient Information **Patient Name** S2  **DOB**  **Sex** Unknown  **MRN** | Reference Information **Ordering Physician**  **Order Date**  **Contact/Recipient**  **Additional** | Sample Information **Specimen Site**  **Collection Date**  **Received Date**  **Accession #** |

## **About the Test**

Golden Labs utilizes a Next Generation Sequencing (NGS) based assay of cancer-related genes to detect relevant genomic alterations that provide therapeutic guidance, disease diagnostic evidence or prognostic indication. See Methods and Limitations.

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| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Results Summary**  **Negative Findings**  No pathogenic single nucleotide variants, indels, copy number changes, or structural variations found for:  | **ALK** | **ROS1** |   |  |  | | --- | --- | | **Genomic Finding** | **Number of Findings Detected** | | Genomic Findings with Clinical Evidence | 1 | | Genomic Findings with Prognostic/Diagnostic Evidence | 1 | | Variants with Potential Significance | 0 | | Germline Alterations | 0 | |
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# **Genomic findings with Evidence of Clinical Significance**

## **Genomic Findings with Clinical Evidence**

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| --- | --- | --- | --- | --- |
| Genomic Finding | FDA-Approved Therapies  in Patient’s Tumor Type | Therapies of Potential Significance | Resistance | Potential Clinical Trials |
|  | Afatinib, Atezolizumab, Bevacizumab, Durvalumab, Necitumumab, Nivolumab, Ramucirumab (1A) Atezolizumab, Durvalumab, Nivolumab (1A) Atezolizumab, Durvalumab, Nivolumab (1A) Afatinib, Atezolizumab, Bevacizumab, Durvalumab, Necitumumab, Nivolumab, Ramucirumab (1A) | None | None | Yes, see clinical trials section |
| EGFR T790M | Osimertinib (1A) Osimertinib (1A) | None | Afatinib, Dacomitinib, Erlotinib, Gefitinib (1A) | Yes, see clinical trials section |

## **Genomic Findings with Prognostic or Diagnostic Evidence**

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| --- | --- | --- | --- |
| Gene | Description | Location | Evidence |
| *EGFR* | Thr790Met | Exon 20 | Prognostic Tier III |

## **Other Reported Biomarkers**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| |  |  |  | | --- | --- | --- | | Gene | Type | Description | | *ALK* | Gene mutation | Negative Finding | | |  |  |  | | --- | --- | --- | | Gene | Type | Description | | *ROS1* | Gene mutation | Negative Finding | |

**Genomic Finding Details**

|  |  |
| --- | --- |
| Sensitivity to Drugs:  Tier I - Level A  Afatinib Atezolizumab Bevacizumab Durvalumab Necitumumab Nivolumab Ramucirumab  Tier I - Level A  Atezolizumab Durvalumab Nivolumab  Tier I - Level A  Atezolizumab Durvalumab Nivolumab  Tier I - Level A  Afatinib Atezolizumab Bevacizumab Durvalumab Necitumumab Nivolumab Ramucirumab  Resistance to Drugs:  None  Biomarker(s): | **Drug Sensitivity:**  *Tier I - Level A*  The following targeted therapies are FDA/EMA approved and/or recommended by NCCN guidelines for the treatment of patients with non-small cell lung cancer with resectable or unresectable/metastatic tumors, of squamous and/or non-squamous histology, whose diseases were stable after chemotherapy or progressed on or following chemotherapy or treatment with EGFR/ALK inhibitors (NCCN Guidelines for Non-Small Cell Lung Cancer). These therapies are administered either as monotherapy or in association with chemotherapy, depending on the medication.   Atezolizumab (Tecentriq) (PMID: 27979383), durvalumab (Imfinzi) (PMID: 28885881, 30280658, 32209338, 33583206, 34731446), and nivolumab (Opdivo) (PMID: 35403841, 26028407, 26412456, 29023213, 33449799) are injectable immune checkpoint inhibitor monoclonal antibodies that inhibit PD-L1 (PMID: 34937915, 28878676). Ramucirumab (Cyramza) is an injectable monoclonal antibody that selectively targets KDR (VEGFR2) (PMID: 23718298, 30314524, 27306885, 29191593, 24933332).  Certain patients with non-squamous non-small cell lung cancer can also be treated with bevacizumab (Avastin), an injectable humanized mAb that functions as an angiogenesis inhibitor by targeting VEGF (PMID: 23419196, 20688807, 32335505, 17167137, 17602060, 33725344, 20150572).  Patients with squamous non-small cell lung cancer may also qualify for treatment with the following FDA-approved drugs: afatinib (Gilotrif), pembrolizumab (Keytruda) and necitumumab (Portrazza). Afatinib is a tyrosine kinase inhibitor that irreversibly inhibits the ERBB/HER family of receptors, including EGFR (PMID: 30392436, 29902295, 26156651, 33061419). Pembrolizumab is an injectable immune checkpoint inhibitor monoclonal antibody that inhibits the PD-1 receptor (PMID: 34937915, 31432705, 30280635, 31751163). Necitumumab is a monoclonal antibody with antagonist activity towards EGFR (PMID: 18275813, 30025476, 26045340, 26980471). The NCCN guidelines recommend against the use of necitumumab in squamous non-small cell lung cancer due to toxicity, cost and limited improvement in the efficacy of the combination therapy compared to the chemotherapy regimen alone (NCCN Guidelines for Non-Small Cell Lung Cancer).  Tier I - Level A  Atezolizumab (Tecentriq), durvalumab (Imfinzi) and nivolumab (Opdivo) are injectable immune checkpoint inhibitor monoclonal antibodies that inhibit PD-L1 (PMID: 34937915, 34731446, 28878676). Atezolizumab is FDA approved as a single agent for the treatment of metastatic NSCLC patients who have disease progression during or after chemotherapy (PMID: 27979383). Durvalumab is indicated for patients with unresectable NSCLC whose disease has not progressed following chemoradiotherapy (PMID: 28885881, 30280658, 32209338, 33583206). Nivolumab is FDA approved in combination with chemotherapy as neoadjuvant treatment of adult patients with resectable NSCLC (PMID: 35403841). It is also indicated as a single agent for the treatment of patients with metastatic NSCLC with progression on or after platinum-based chemotherapy (PMID: 26028407, 33449799).  Tier I - Level A  Atezolizumab (Tecentriq), durvalumab (Imfinzi) and nivolumab (Opdivo) are injectable immune checkpoint inhibitor monoclonal antibodies that inhibit PD-L1 (PMID: 34937915, 34731446, 28878676). Atezolizumab is FDA approved as a single agent for the treatment of metastatic NSCLC patients who have disease progression during or after chemotherapy (PMID: 27979383). Durvalumab is indicated for patients with unresectable NSCLC whose disease has not progressed following chemoradiotherapy (PMID: 28885881, 30280658, 32209338, 33583206). Nivolumab is FDA approved in combination with chemotherapy as neoadjuvant treatment of adult patients with resectable NSCLC (PMID: 35403841). It is also indicated as a single agent for the treatment of patients with metastatic NSCLC with progression on or after platinum-based chemotherapy (PMID: 26028407, 33449799).  Tier I - Level A  The following targeted therapies are FDA/EMA approved and/or recommended by NCCN guidelines for the treatment of patients with non-small cell lung cancer with resectable or unresectable/metastatic tumors, of squamous and/or non-squamous histology, whose diseases were stable after chemotherapy or progressed on or following chemotherapy or treatment with EGFR/ALK inhibitors (NCCN Guidelines for Non-Small Cell Lung Cancer). These therapies are administered either as monotherapy or in association with chemotherapy, depending on the medication.   Atezolizumab (Tecentriq) (PMID: 27979383), durvalumab (Imfinzi) (PMID: 28885881, 30280658, 32209338, 33583206, 34731446), and nivolumab (Opdivo) (PMID: 35403841, 26028407, 26412456, 29023213, 33449799) are injectable immune checkpoint inhibitor monoclonal antibodies that inhibit PD-L1 (PMID: 34937915, 28878676). Ramucirumab (Cyramza) is an injectable monoclonal antibody that selectively targets KDR (VEGFR2) (PMID: 23718298, 30314524, 27306885, 29191593, 24933332).  Certain patients with non-squamous non-small cell lung cancer can also be treated with bevacizumab (Avastin), an injectable humanized mAb that functions as an angiogenesis inhibitor by targeting VEGF (PMID: 23419196, 20688807, 32335505, 17167137, 17602060, 33725344, 20150572).  Patients with squamous non-small cell lung cancer may also qualify for treatment with the following FDA-approved drugs: afatinib (Gilotrif), pembrolizumab (Keytruda) and necitumumab (Portrazza). Afatinib is a tyrosine kinase inhibitor that irreversibly inhibits the ERBB/HER family of receptors, including EGFR (PMID: 30392436, 29902295, 26156651, 33061419). Pembrolizumab is an injectable immune checkpoint inhibitor monoclonal antibody that inhibits the PD-1 receptor (PMID: 34937915, 31432705, 30280635, 31751163). Necitumumab is a monoclonal antibody with antagonist activity towards EGFR (PMID: 18275813, 30025476, 26045340, 26980471). The NCCN guidelines recommend against the use of necitumumab in squamous non-small cell lung cancer due to toxicity, cost and limited improvement in the efficacy of the combination therapy compared to the chemotherapy regimen alone (NCCN Guidelines for Non-Small Cell Lung Cancer). |
| Sensitivity to Drugs:  Tier I - Level A  Osimertinib  Tier I - Level A  Osimertinib  Resistance to Drugs:  Tier I - Level A  Afatinib Dacomitinib Erlotinib Gefitinib  Biomarker(s):  EGFR T790M | **EGFR T790M Drug Sensitivity:**  *Tier I - Level A*  Osimertinib (Tagrisso) is a third-generation EGFR tyrosine kinase inhibitor (TKI) that is active against several EGFR alterations, including Ex19del, p.L858R and the resistance mutation p.T790M (PMID: 24893891, 33392095). Osimertinib is the only FDA-approved EGFR TKI indicated for treating adult patients with metastatic non-small cell lung cancer (NSCLC) harboring *EGFR p.T790M* mutationswhose disease has progressed on or after EGFR TKI therapy (PMID: 27959700, 30527177, 32861806). Relative to standard chemotherapy, osimertinib demonstrated superior response rates, prolonged median progression-free survival, and improved quality of life in *EGFR*-mutant advanced NSCLC patients previously treated with first- or second-generation EGFR TKIs, especially in patients whose tumors harbored the *EGFR p.T790M* resistance mutation (PMID: 25923549, 28221867, 27959700, 29151359, 29320658).  Tier I - Level A  Osimertinib (Tagrisso) is a third-generation EGFR tyrosine kinase inhibitor (TKI) that is active against several EGFR alterations, including Ex19del, p.L858R and the resistance mutation p.T790M (PMID: 24893891, 33392095). Osimertinib is the only FDA-approved EGFR TKI indicated for treating adult patients with metastatic non-small cell lung cancer (NSCLC) harboring *EGFR p.T790M* mutationswhose disease has progressed on or after EGFR TKI therapy (PMID: 27959700, 30527177, 32861806). Relative to standard chemotherapy, osimertinib demonstrated superior response rates, prolonged median progression-free survival, and improved quality of life in *EGFR*-mutant advanced NSCLC patients previously treated with first- or second-generation EGFR TKIs, especially in patients whose tumors harbored the *EGFR p.T790M* resistance mutation (PMID: 25923549, 28221867, 27959700, 29151359, 29320658).  **EGFR T790M Drug Resistance:**  *Tier I - Level A*  Erlotinib (Tarceva), gefitinib (Iressa), afatinib (Gilotrif), and dacomitinib (Vizimpro) are first- and second-generation EGFR tyrosine kinase inhibitors (TKIs) that are FDA approved as first-line treatment options for patients with metastatic non-small cell lung cancer (NSCLC) with *EGFR* Ex19del or p.L858R substitution mutations. Acquired resistance occurs in virtually all NSCLC patients who initially respond to first- or second-generation EGFR TKI therapy. The *EGFR* p.T790M gatekeeper mutation confers resistance to first- and second-generation EGFR TKIs and is the most common mechanism of acquired resistance in NSCLC, occurring in approximately 60% of NSCLC patients who progress or relapse on first-line therapy (PMID: 23470965, 28149837).  **EGFR T790M Biomarker Summary:**  *EGFR* p.T790M is an exon 20 missense mutation that is associated with acquired resistance to EGFR tyrosine kinase inhibitor (TKI) therapy in non-small cell lung cancer (NSCLC). *EGFR* p.T790M has been reported as an acquired mutation in approximately 60% of NSCLC patients with disease progression after initial response to first- or second-generation EGFR TKIs (PMID: 25979928, 23470965, 25271963, 24101047, 15737014, 17020982, 19589612). Within the EGFR ATP binding pocket, codon Thr790 represents a “gatekeeper” residue that regulates TKI binding. The precise mechanisms of *EGFR* p.T790M resistance remain unclear, although preclinical studies suggest that this mutation confers TKI resistance by increasing EGFR affinity for ATP and/or sterically hindering TKI binding to EGFR (PMID: 18227510, 15728811, 15897464, 17020982). The *EGFR* p.T790M mutation is generally detected together with *EGFR* sensitizing mutations such as exon 19 deletions (Ex19del) or p.L858R (PMID: 31562956, 30108370). In very rare cases (~0.5% of never-smokers with NSCLC), *EGFR* p.T790M has been identified in treatment-naïve NSCLC patients; in this context, *EGFR* p.T790M may be a germline mutation that is associated with predisposition to familial lung cancer (PMID: 16258541, 22588155, 24736066).  **Technical Data for EGFR T790M:**   |  |  | | --- | --- | | Transcript and Coding Change | NM\_005228.5:c.2369C>T (p.Thr790Met) | | Location | 7:55249071 | | Human Genome (GRCh37) | NC\_000007.13: g.55249071C>T | | Human Genome (GRCh38) | NC\_000007.14: g.55181378C>T | | dbSNP Identifier | rs121434569 | | ClinVar Variant ID | 16613 | | COSMIC Mutation ID | COSM6240 | | African Allele Frequency | 2/16256 (0.01%) | |

**Prognostic and Diagnostic Details**

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| --- | --- |
| Prognostic Evidence:  Tier III  Diagnostic Evidence:  None | **EGFR Thr790Met Prognostic Evidence:**  *EGFR* p.T790M is most commonly seen as an acquired resistance mutation in non-small cell lung cancer (NSCLC) patients treated with EGFR tyrosine kinase inhibitors (TKI). When present as a de novo mutation, *EGFR* p.T790M is associated with lower response rate, shorter progression-free survival on EGFR TKI, and shorter overall survival (PMID: 24478319, 22215752, 21233402). |

**Therapeutic Options Details**

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| ***Durvalumab***  FDA Approved Therapy For Patient Tumor Type  Approved for:  Non-Small Cell Lung Cancer, Small Cell Lung Cancer, Biliary Tract Cancer  Relevant Biomarker:  Commercial Labels:  Imfinzi | **Drug Class:** Monoclonal Antibody, Immune Checkpoint Inhibitor  **Mechanism of Action:** PD-L1  **Indication for Use:** Durvalumab (Imfinzi) is FDA approved for the treatment of certain patients with extensive-stage small cell lung cancer (PMID: 34731446, 33687763) or non-small cell lung cancer (PMID: 32764980). It is also approved in combination with gemcitabine and cisplatin for the treatment of adult patients with locally advanced or metastatic biliary tract cancer (https://evidence.nejm.org/doi/full/10.1056/EVIDoa2200015).  **Durvalumab Description:** Durvalumab is an injectable monoclonal antibody that belongs to the class of drugs called immune checkpoint inhibitors (PMID: 34731446). Durvalumab targets PD-L1, an essential immune checkpoint protein that is often upregulated in cancer cells as a mechanism of immune evasion (PMID: 28878676).  **Resistance:** Durvalumab is an injectable monoclonal antibody that belongs to the class of drugs called immune checkpoint inhibitors (PMID: 34731446). Durvalumab targets PD-L1, an essential immune checkpoint protein that is often upregulated in cancer cells as a mechanism of immune evasion (PMID: 28878676). |
| ***Nivolumab***  FDA Approved Therapy For Patient Tumor Type  Approved for:  Melanoma, Non-Small Cell Lung Cancer, Malignant Pleural Mesothelioma, Renal Cell Carcinoma, Classical Hodgkin Lymphoma, Squamous Cell Carcinoma of the Head and Neck, Urothelial Carcinoma, Colorectal Cancer, Hepatocellular Carcinoma, Esophageal Cancer, Gastric Cancer  Relevant Biomarker:  Commercial Labels:  Opdivo | **Drug Class:** Monoclonal Antibody, Immune Checkpoint Inhibitor  **Mechanism of Action:** PD-1  **Indication for Use:** Nivolumab (Opdivo) is FDA approved for diverse cancer types, including for the treatment of certain patients with melanoma, non-small cell lung cancer, malignant pleural mesothelioma, renal cell carcinoma, classical Hodgkin lymphoma, head and neck squamous cell carcinoma, urothelial carcinoma, colorectal cancer, hepatocellular carcinoma, and gastroesophageal cancers.  **Nivolumab Description:** Nivolumab is an injectable fully-humanized monoclonal antibody that belongs to the class of drugs called immune checkpoint inhibitors. Nivolumab inhibits PD-1, an immune checkpoint receptor that is expressed on T cells and functions as a negative regulator of T-cell activation (PMID: 34937915). Nivolumab blocks PD-1 interaction with its ligands PD-L1 (CD274) and PD-L2 (CD273), resulting in enhanced T-cell activation and improved antitumor immune responses (PMID: 34937915).  **Resistance:** Disease progression after treatment with immune checkpoint inhibitors, including nivolumab, may occur due to diverse mechanisms, including a decrease in antigen presence and presentation, or an increase in immune suppression mediated by the tumor and the tumor microenvironment (PMID: 35276342). |
| ***Afatinib***  FDA Approved Therapy For Patient Tumor Type  Approved for:  Non-Small Cell Lung Cancer  Relevant Biomarker:  EGFR T790M  Commercial Labels:  Gilotrif | **Drug Class:** Kinase Inhibitor  **Mechanism of Action:** ERBB2, ERBB4  **Indication for Use:** Afatinib (Gilotrif) is approved by the FDA as a first-line treatment for patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have non-resistant *EGFR* mutations as detected by an FDA-approved test, including classical *EGFR* Ex19del or p.L858R activating mutations and uncommon sensitizing EGFR mutations such as p.G719X, p.S768I, and p.L861Q. Afatinib is also indicated for the treatment of patients with metastatic squamous NSCLC that has progressed following platinum-based chemotherapy.  **Afatinib Description:** Afatinib is an oral second-generation EGFR tyrosine kinase inhibitor (TKI) that targets the ERBB/HER family of receptors, including EGFR, ERBB2, and ERBB4 (PMID: 23493883). Afatinib covalently and irreversibly binds to the ATP-binding site of its target kinase (PMID: 18408761, 23493883).  **Resistance:** Diverse *EGFR*-dependent and *EGFR*-independent mechanisms of acquired resistance to first- and second-generation EGFR TKIs have been described (PMID: 28149837, 34638411). Common *EGFR*-independent mechanisms include acquired *MET* or *ERBB2* amplification, *ALK* or *ROS1* oncogenic fusions, hyperactivation of the MAPK and PI3K signaling pathways, epithelial mesenchymal transition and/or histologic transformation of non-small cell lung cancer to small cell lung cancer (PMID: 28149837, 34638411). The most common *EGFR*-dependent mechanism of afatinib resistance is acquisition of the *EGFR* p.T790M gatekeeper mutation, which occurs in approximately 60% of NSCLC patients who progress or relapse on first-line therapy (PMID: 23470965, 28149837). |
| ***Atezolizumab***  FDA Approved Therapy For Patient Tumor Type  Approved for:  Urothelial Carcinoma, Non-Small Cell Lung Cancer, Small Cell Lung Cancer, Hepatocellular Carcinoma, Melanoma  Relevant Biomarker:  Commercial Labels:  Tecentriq | **Drug Class:** Monoclonal Antibody, Immune Checkpoint Inhibitor  **Mechanism of Action:** PD-L1  **Indication for Use:** Atezolizumab (Tecentriq) is FDA approved as a single-agent for the treatment of certain patients with urothelial cancer (PMID: 34184561, 33401585) and non-small cell lung cancer (NSCLC) (PMID: 35101885, 34104805). Atezolizumab is also approved to treat several cancer types as part of combination therapies with chemotherapy, targeted therapies, angiogenesis inhibitors, and others (PMID: 35062949, 31829747, 33427656, 35032007, 34956912, 35081747, 32534646, 35131452).  **Atezolizumab Description:** Atezolizumab is an injectable monoclonal antibody that belongs to the class of drugs called immune checkpoint inhibitors (PMID: 33256089). Atezolizumab targets PD-L1, an essential immune checkpoint protein that is often upregulated in cancer cells as a mechanism of immune evasion (PMID: 28878676).  **Resistance:** Disease progression after treatment with immune checkpoint inhibitors, including atezolizumab, may occur due to diverse mechanisms, including a decrease in antigen presence and presentation, or an increase in immune suppression mediated by the tumor and the tumor microenvironment (PMID: 35276342). |
| ***Bevacizumab***  FDA Approved Therapy For Patient Tumor Type  Approved for:  Bowel, Peritoneal Neoplasm, Renal Cell Carcinoma, Glioblastoma, Non-Small Cell Lung Cancer, Ovarian Carcinoma, Cervical Carcinoma, Breast Carcinoma, Digestive System Neoplasm  Relevant Biomarker:  Commercial Labels:  Mvasi, Avastin, Lextemy, Aybintio, Zirabev, Onbevzi, Oyavas, Equidacent, Bambevi, Abevmy, Alymsys | **Drug Class:** Monoclonal Antibody  **Mechanism of Action:** VEGF  **Indication for Use:** Bevacizumab (Avastin) is FDA approved for single agent treatment or with chemotherapy for patients with various cancer types, including adults with recurrent glioblastoma that has progressed following prior therapy (PMID: 19897538), or persistent, recurrent, or metastatic cervical cancer (PMID: 27748633), among others (PMID: 15901587, 17602060, 20061402, 24687829, 28438473, 32305099, 22204724, 31216226).Bevacizumab (Avastin) is also FDA approved as a combination therapy with atezolizumab (Tecentriq), an immune checkpoint inhibitor, and paclitaxel + carboplatin chemotherapy for first-line treatment of patients with metastatic non-squamous, non-small cell lung cancer with no EGFR or ALK genomic tumor aberrations (PMID: 29863955). Bevacizumab is also FDA approved as a combination therapy with atezolizumab for treatment of patients with unresectable or metastatic hepatocellular carcinoma who have not received prior systemic therapy (PMID: 34051880, 34189869). Bevacizumab is also FDA approved as a combination therapy with pembrolizumab, an immune checkpoint inhibitor, for treatment of patients with persistent, recurrent or metastatic cervical cancer whose tumors express PD-L1 (Combined Positive Score [CPS] ≥1) as determined by an FDA-approved test (PMID: 34534429).  **Bevacizumab Description:** Bevacizumab is a humanized anti-vascular endothelial-derived growth factor (anti-VEGF) monoclonal antibody administered by injection that functions as an angiogenesis inhibitor (PMID: 23419196, 20688807). Bevacizumab binds to circulating VEGF and blocks VEGF-receptor interaction, thereby preventing VEGF-mediated downstream signaling that promotes angiogenesis and tumor growth (PMID: 11970755, 25568148). The result is lower tissue interstitial pressure, increased vascular permeability, and increased apoptosis of tumor endothelial cells (PMID: 17212999).  **Resistance:** Disease progression in cancer patients treated with bevacizumab occurs by resistance mechanisms that are not fully elucidated, but appear to involve a return to hypoxic conditions that favor expression of pro-angiogenic factors such as VEGF and PDGF, and restoration of aberrant angiogenesis required to support tumor growth (PMID: 28386777, 32175278). These mechanisms may involve reestablishment of VEGF signaling and/or activation of alternative angiogenic pathways (28386777, 30253191). |
| ***Necitumumab***  FDA Approved Therapy For Patient Tumor Type  Approved for:  Squamous Non-Small Cell Lung Cancer  Relevant Biomarker:  Commercial Labels:  Portrazza | **Drug Class:** Monoclonal Antibody  **Mechanism of Action:**  EGFR  **Indication for Use:** The FDA approved the use of necitumumab (Portrazza) in combination with chemotherapy for first-line treatment of patients with metastatic squamous non-small cell lung cancer (PMID:26045340, 26980471).  **Necitumumab Description:** Necitumumab (Portrazza) is an injectable fully human monoclonal antibody with antagonistic activity towards the epidermal growth factor receptor (EGFR) (PMID: 30075697, 33188892, 30025476). It binds to the extracellular domain of EGFR, blocking the interaction with endogenous ligands. As a result, necitumumab inhibits downstream pathways that lead to enhanced apoptosis and reduced cell proliferation, angiogenesis, invasiveness and metastasis (PMID: 20197484, 18275813).  **Resistance:** Disease progression after treatment with necitumumab may occur due to EGFR/EGFR ligand overexpression, mutations in EGFR, or activation of alternative signaling pathways, among others (PMID: 31228284, 32793499). |
| ***Ramucirumab***  FDA Approved Therapy For Patient Tumor Type  Approved for:  Gastric or Gastro-Esophageal Junction Adenocarcinoma, Non-Small Cell Lung Cancer, Colorectal Cancer, and Hepatocellular Carcinoma  Relevant Biomarker:  Commercial Labels:  Cyramza | **Drug Class:** Monoclonal Antibody  **Mechanism of Action:** KDR (VEGFR2)  **Indication for Use:** Ramucirumab (Cyramza) is FDA/EMA approved as single-agent, or in association with chemotherapy, for patients with various cancer types including advanced or metastatic gastric or gastro-esophageal junction adenocarcinoma, metastatic non-small cell lung cancer (NSCLC), metastatic colorectal cancer, and hepatocellular carcinoma (PMID: 24094768, 25240821, 24933332, 25877855). Ramucirumab is approved in combination with erlotinib (Tarceva) an oral tyrosine kinase inhibitor targeting EGFR, for patients with untreated, EGFR-mutated metastatic NSCLC (PMID: 31591063).  **Ramucirumab Description:** Ramucirumab is an injectable fully human antiangiogenic IgG1 monoclonal antibody that selectively targets KDR (VEGFR2) (PMID: 23718298, 30314524).  Ramucirumab binds to the extracellular domain of KDR with high affinity, blocking interaction with natural ligands VEGFA/C/D (PMID: 32371296).  The result is a reduction in tumor vascularity and growth (PMID: 27306885).  **Resistance:** Disease progression in cancer patients treated with ramucirumab, a selective inhibitor of KDR (VEGFR2)-mediated angiogenesis, has been attributed primarily to angiogenic escape involving compensatory activation of alternate pro-angiogenic pathways that include receptors FLT1 (VEGFR1), FLT4 (VEGFR3), PDGFR and FGFR, among others (PMID: 23803182, 27306885). |
| ***Osimertinib***  FDA Approved Therapy For Patient Tumor Type  Approved for:  Non-Small Cell Lung Cancer  Relevant Biomarker:  EGFR T790M  Commercial Labels:  Tagrisso | **Drug Class:** Kinase Inhibitor  **Mechanism of Action:** EGFR p.T790M  **Indication for Use:** Osimertinib (Tagrisso) is FDA approved as a first-line treatment for patients with unresectable or metastatic non-small cell lung cancer (NSCLC) whose tumors harbor *EGFR* Ex19del or p.L858R mutations and is the preferred first-line therapy for NSCLC patients with *EGFR* sensitizing mutations (NCCN Guidelines for NSCLC). It is also indicated for the treatment of patients with *EGFR* p.T790M mutation-positive NSCLC who have progressed on or after prior EGFR tyrosine kinase inhibitor (TKI) therapy and as an adjuvant treatment after tumor resection in patients with early-stage NSCLC whose tumors have *EGFR* Ex19del or p.L858R mutations.  **Osimertinib Description:** Osimertinib is a third-generation EGFR TKI that selectively inhibits sensitizing *EGFR* mutations and the common *EGFR* p.T790M gatekeeper resistance mutation with minimal activity against wild-type EGFR (PMID: 24893891, 33392095). Osimertinib irreversibly inhibits EGFR by forming a covalent bond with *EGFR* codon Cys797 within the ATP binding site of mutant EGFR (PMID: 24893891).  **Resistance:** Diverse *EGFR*-dependent and *EGFR*-independent mechanisms of osimertinib resistance have been described (PMID: 31564718). Common *EGFR*-independent mechanisms include acquired *MET* or *ERBB2* amplification, *ALK* or *ROS1* oncogenic fusions, hyperactivation of the MAPK and PI3K signaling pathways, epithelial-mesenchymal transition and/or histologic transformation of non-small cell lung cancer to small cell lung cancer (PMID: 31564718). The most common *EGFR*-dependent mechanism of simertinib resistance is the acquisition of missense substitutions at *EGFR* codon Cys797, which block simertinib binding to the EGFR kinase domain (PMID: 30128066, 31564718). |
| ***Dacomitinib***  Therapy of Potential Significance  Approved for:  Non-Small Cell Lung Cancer  Relevant Biomarker:  EGFR T790M  Commercial Labels:  Vizimpro | **Drug Class:** Kinase Inhibitor  **Mechanism of Action:** EGFR, ERBB2, ERBB4  **Indication for Use:** Dacomitinib (Vizimpro) is approved by the FDA as a first-line treatment for patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have *EGFR* exon 19 deletion (Ex19del) or p.L858R mutations.  **Dacomitinib Description:** Dacomitinib is an oral second-generation EGFR tyrosine kinase inhibitor (TKI) that targets the ERBB/HER family of receptors, including EGFR, ERBB2, and ERBB4 (PMID: 23493883). Dacomitinib covalently and irreversibly binds to the ATP-binding site of its target kinase (PMID: 18089823, 23493883).  **Resistance:** Diverse *EGFR*-dependent and *EGFR*-independent mechanisms of acquired resistance to first- and second-generation EGFR TKIs have been described (PMID: 28149837, 34638411). Common *EGFR*-independent mechanisms include acquired *MET* or *ERBB2* amplification, *ALK* or *ROS1* oncogenic fusions, hyperactivation of the MAPK and PI3K signaling pathways, epithelial mesenchymal transition and/or histologic transformation of non-small cell lung cancer to small cell lung cancer (PMID: 28149837, 34638411). The most common *EGFR*-dependent mechanism of dacomitinib resistance is acquisition of the *EGFR* p.T790M gatekeeper mutation, which occurs in approximately 60% of NSCLC patients who progress or relapse on first-line therapy (PMID: 23470965, 28149837). |
| ***Erlotinib***  Therapy of Potential Significance  Approved for:  Non-Small Cell Lung Cancer, Pancreatic Cancer  Relevant Biomarker:  EGFR T790M  Commercial Labels:  Tarceva | **Drug Class:** Kinase Inhibitor  **Mechanism of Action:** EGFR  **Indication for Use:** Erlotinib (Tarceva) is FDA approved for the treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have *EGFR* exon 19 deletions (Ex19del) or the exon 21 p.L858R substitution and are receiving first-line, maintenance, or second- or greater-line treatment after progression on at least one prior chemotherapy regimen. Erlotinib is also indicated in combination with gemcitabine as a first-line treatment for patients with locally advanced, unresectable, or metastatic pancreatic cancer.  **Erlotinib Description:** Erlotinib is an oral first-generation EGFR tyrosine kinase inhibitor (TKI) that binds competitively and reversibly to the ATP-binding site of the EGFR tyrosine kinase domain (PMID: 12850190).  **Resistance:** Diverse *EGFR*-dependent and *EGFR*-independent mechanisms of acquired resistance to first- and second-generation EGFR TKIs have been described (PMID: 28149837, 34638411). Common *EGFR*-independent mechanisms include acquired *MET* or *ERBB2* amplification, *ALK* or *ROS1* oncogenic fusions, hyperactivation of the MAPK and PI3K signaling pathways, epithelial-mesenchymal transition and/or histologic transformation of non-small cell lung cancer to small cell lung cancer (PMID: 28149837, 34638411). The most common *EGFR*-dependent mechanism of erlotinib resistance is acquisition of the *EGFR* p.T790M gatekeeper mutation, which occurs in approximately 60% of NSCLC patients who progress or relapse on first-line therapy (PMID: 23470965, 28149837). |
| ***Gefitinib***  Therapy of Potential Significance  Approved for:  Non-Small Cell Lung Cancer  Relevant Biomarker:  EGFR T790M  Commercial Labels:  Iressa | **Drug Class:** Kinase Inhibitor  **Mechanism of Action:** EGFR  **Indication for Use:** Gefitinib (Iressa) is FDA approved for the first-line treatment of patients with metastatic non-small cell lung cancer (NSCLC) whose tumors have *EGFR* exon 19 deletions (Ex19del) or the exon 21 p.L858R substitution, as detected by an FDA-approved test.  **Gefitinib Description:** Gefitinib is an oral first-generation EGFR tyrosine kinase inhibitor (TKI) that binds competitively and reversibly to the ATP-binding site of the EGFR tyrosine kinase domain (PMID: 12850190).  **Resistance:** Diverse *EGFR*-dependent and *EGFR*-independent mechanisms of acquired resistance to first- and second-generation EGFR TKIs have been described (PMID: 28149837, 34638411). Common *EGFR*-independent mechanisms include acquired *MET* or *ERBB2* amplification, *ALK* or *ROS1* oncogenic fusions, hyperactivation of the MAPK and PI3K signaling pathways, epithelial-mesenchymal transition and/or histologic transformation of non-small cell lung cancer to small cell lung cancer (PMID: 28149837, 34638411). The most common *EGFR*-dependent mechanism of gefitinib resistance is acquisition of the *EGFR* p.T790M gatekeeper mutation, which occurs in approximately 60% of NSCLC patients who progress or relapse on first-line therapy (PMID: 23470965, 28149837). |

**Relevant Clinical Trials**

## **Clinical Trials Summary**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| Genomic Finding | Type | NCT ID | Drugs | Phase |
|  |  | NCT04925284  NCT03178552  NCT03845166  NCT03811002  NCT05091567  NCT03782207 | Nivolumab, Bevacizumab  Atezolizumab, Bevacizumab  Atezolizumab  Atezolizumab  Atezolizumab  Atezolizumab | I  II/III  I  II/III  III |
| EGFR T790M | Mutation | NCT03831932  NCT04811001 | Osimertinib  Osimertinib, Dacomitinib | I/II  II |

|  |  |
| --- | --- |
| ***NCT04925284***  Started: June 7, 2021 Ends: October 7, 2024  Phase: I  Relevant Therapy:  Nivolumab  Bevacizumab  Relevant Biomarker: | **Study of XB002 in Subjects With Solid Tumors (JEWEL-101)**  This is a Phase 1, open-label, multicenter, dose-escalation and expansion study evaluating the safety, tolerability, PK, pharmacodynamics, and clinical antitumor activity of XB002 administered IV q3w alone and in combination with nivolumab or bevacizumab to subjects with advanced solid tumors.  **Eligibility:** Age 18 Years+, Male or Female |
| ***NCT03178552***  Started: September 22, 2017 Ends: April 27, 2024  Phase: II/III  Relevant Therapy:  Atezolizumab  Bevacizumab  Relevant Biomarker: | **A Study to Evaluate the Efficacy and Safety of Multiple Targeted Therapies as Treatments for Participants With Non-Small Cell Lung Cancer (NSCLC)**  This is a phase 2/3, global, multicenter, open-label, multi-cohort study designed to evaluate the safety and efficacy of targeted therapies or immunotherapy as single agents or in combination in participants with unresectable, advanced or metastatic NSCLC determined to harbor oncogenic somatic mutations or positive by tumor mutational burden (TMB) assay as identified by two blood-based next-generation sequencing (NGS) circulating tumor DNA (ctDNA) assays.  **Eligibility:** Age 18 Years+, Male or Female |
| ***NCT03845166***  Started: March 20, 2019 Ends: November 2024  Phase: I  Relevant Therapy:  Atezolizumab  Relevant Biomarker: | **A Study of XL092 as Single-Agent and Combination Therapy in Subjects With Solid Tumors**  This is a Phase 1, open-label, dose-escalation and expansion study, evaluating the safety, tolerability, pharmacokinetics (PK), preliminary antitumor activity, and effect on biomarkers of XL092 administered alone, in combination with atezolizumab, and in combination with avelumab to subjects with advanced solid tumors.  **Eligibility:** Age 18 Years+, Male or Female |
| ***NCT03811002***  Started: May 28, 2019 Ends: December 28, 2026  Phase: II/III  Relevant Therapy:  Atezolizumab  Relevant Biomarker: | **Testing the Addition of a New Immunotherapy Drug, Atezolizumab (MPDL3280A), to the Usual Chemoradiation (CRT) Therapy Treatment for Limited Stage Small Cell Lung Cancer (LS-SCLC)**  This phase II/III trial studies how well chemotherapy and radiation therapy (chemoradiation) with or without atezolizumab works in treating patients with limited stage small cell lung cancer. Drugs used in chemotherapy, such as etoposide, cisplatin, and carboplatin, work in different ways to stop the growth of tumor cells, either by killing the cells, by stopping them from dividing, or by stopping them from spreading. Radiation therapy uses high energy x-rays to kill tumor cells and shrink tumors. Immunotherapy with monoclonal antibodies, such as atezolizumab, may help the body's immune system attack the cancer, and may interfere with the ability of tumor cells to grow and spread. Giving chemoradiation with or without atezolizumab may work better in treating patients with limited stage small cell lung cancer.  **Eligibility:** Age 18 Years+, Male or Female |
| ***NCT03831932***  Started: May 2, 2019 Ends: June 1, 2023  Phase: I/II  Relevant Therapy:  Osimertinib  Relevant Biomarker:  EGFR T790M | **Telaglenastat Hydrochloride and Osimertinib in Treating Patients With EGFR-Mutated Stage IV Non-small Cell Lung Cancer**  This phase Ib trial studies the side effects and best dose of telaglenastat hydrochloride when given together with osimertinib in treating patients with stage IV non-small cell lung cancer and a mutation in the EGFR gene. Telaglenastat hydrochloride and osimertinib may stop the growth of tumor cells by blocking some of the enzymes needed for cell growth.  **Eligibility:** Age 18 Years+, Male or Female |
| ***NCT04811001***  Started: June 12, 2020 Ends: December 31, 2023  Phase: II  Relevant Therapy:  Osimertinib  Dacomitinib  Relevant Biomarker:  EGFR T790M | **Best EGFR-TKI Sequence in NSCLC Harboring EGFR Mutations**  The best drug sequencing of dacomitinib or osimertinib in patients with advanced or metastatic Epidermal Growth Factor Receptor (EGFR) mutation positive non-small-cell lung cancer (NSCLC) has not yet been determined. The study enables investigation of the efficacy of dacomitinib followed by or subsequent to osimertinib osimertinib in patients with classical or uncommon activating EGFR mutations. Efficacy of dacomitinib will be defined in patients with asymptomatic or controlled brain metastases, special population eligible in this clinical trial.  **Eligibility:** Age 18 Years+, Male or Female  **Nearby Sites:**  Novara, N/A **A.O.U. "Maggiore della Carità** Contact: undefined  Phone: undefined |
| ***NCT05091567***  Started: November 18, 2021 Ends: March 6, 2026  Phase: III  Relevant Therapy:  Atezolizumab  Relevant Biomarker: | **A Phase III, Open-Label Study of Maintenance Lurbinectedin in Combination With Atezolizumab Compared With Atezolizumab in Participants With Extensive-Stage Small-Cell Lung Cancer**  Study GO43104 is a Phase III, randomized, open-label, multicenter study of lurbinectedin in combination with atezolizumab compared with atezolizumab alone administered as maintenance therapy in participants with extensive-stage small-cell lung cancer (ES-SCLC) after first-line induction therapy with carboplatin, etoposide, and atezolizumab. The study consists of 2 phases: an induction phase and a maintenance phase. Participants need to have an ongoing response or stable disease per the Response Evaluation Criteria in Solid Tumor (RECIST) v1.1 criteria after completion of 4 cycles of carboplatin, etoposide, and atezolizumab induction treatment in order to be considered for eligibility screening for the maintenance phase. Eligible participants will be randomized in a 1:1 ratio to receive either lurbinectedin plus atezolizumab or atezolizumab in the maintenance phase.  **Eligibility:** Age 18 Years+, Male or Female |
| ***NCT03782207***  Started: February 7, 2019 Ends: December 19, 2026  Phase:  Relevant Therapy:  Atezolizumab  Relevant Biomarker: | **A Study Investigating the Outcomes and Safety of Atezolizumab Under Real-World Conditions in Patients Treated in Routine Clinical Practice**  This is a non-interventional, multi-country, multi-centre, multiple cohort prospective study, with retrospective collection of prior medical/treatment history data from medical records, designed to assess the real-world outcomes and safety of atezolizumab for indications in the existing label in the real world setting of routine clinical practice.  **Eligibility:** Age 18 Years+, Male or Female |

**Gene Details**

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| **EGFR Gene Summary:**  *EGFR* (*epidermal growth factor receptor*) encodes a proto-oncogene and cell surface transmembrane glycoprotein. EGFR is a member of the EGFR/ErbB family of tyrosine kinases which also includes ERBB2 (HER2), ERBB3 (HER3), and ERBB4 (PMID: 18259690, 19208461, 22239438, 32219702). EGFR is expressed in tissues of epithelial, mesenchymal, and neuronal origin, and has an important role in regulating normal cellular processes including proliferation, differentiation, development, and survival (PMID: 14666659, 29991287, 35840984). Oncogenic *EGFR* amplification or mutations in the *EGFR* intracellular domain lead to EGFR overexpression and ligand-independent activation of downstream signaling pathways, resulting either directly or indirectly in increased cell proliferation, angiogenesis, invasion, and metastasis (PMID: 25870793, 29991287, 32069320, 35867821). Germline mutations in the *EGFR* kinase domain are associated with a predisposition to lung cancer (PMID: 30225213, 34670806). Somatic *EGFR* alterations have been reported in lung cancer, glioblastoma, and a variety of additional tumor types (cBioPortal, COSMIC). The most common oncogenic EGFR alterations are gene amplification and missense substitutions (cBioPortal, COSMIC).  **EGFR Outcomes & Frequencies:**  *EGFR* is one of the most frequently altered oncogenes in solid tumors (PMID: 16787682). *EGFR* alterations have been reported in diverse human malignancies, including non-small cell lung cancer (NSCLC), glioblastoma, breast, ovarian, gastric, and colon cancer (cBioPortal, COSMIC, PMID: 7612182).*EGFR* overexpression has been reported in 40-89% of patients with NSCLC (PMID: 25870793). *EGFR* mutations, which occur in ~10-15% of Caucasian NSCLC patients and up to 50% of Asian NSCLC patients, are associated with female gender, non-smoking history, and adenocarcinoma histology (PMID: 26609494, 29657128, 25079552, 18948947, 27346245, 22980975, 28336552, 32015526). More than 90% of oncogenic *EGFR* mutations in NSCLC are concentrated in exons 19 and 21 (PMID: 23470965, 34489119). The two most common types of *EGFR* activating mutations are short in-frame deletions in exon 19 that encompass the conserved LREA amino acid sequence at codons 747-750 (45% of NSCLC patients with mutated EGFR) and the exon 21 point mutation p.L858R (40% of NSCLC patients with mutated EGFR); these mutations are referred to as sensitizing *EGFR* mutations and have predictive value for clinical benefit from EGFR-targeted tyrosine kinase inhibitor (TKI) therapy in patients with advanced NSCLC (PMID: 16014883, 25162713, 30608948, 35661118).  Other less common (approximately 10% of NSCLC patients with mutated *EGFR*) *EGFR* mutations are reported throughout exons 18-21, including exon 19 insertions, p.L861Q, p.G719X, and p.S768I, and also confer sensitivity to EGFR TKIs (PMID: 17189394, 28577943, 25870793).Despite predicting responsiveness to EGFR TKIs, sensitizing *EGFR* mutations are not used as prognostic indicator of survival for patients with NSCLC, independent of therapy (PMID: 16014883). Relapse is common following first-line EGFR TKI therapy, and the 5-year overall survival rate for NSCLC patients remains poor, with a survival estimate of 68% for patients with early-stage disease and 0-10% for patients with late-stage disease (PMID: 35337281).  **ALK Gene Summary:**  *ALK* (*anaplastic lymphoma kinase*) is a proto-oncogene that encodes ALK, a receptor tyrosine kinase that belongs to the insulin receptor tyrosine kinase family (PMID: 27468827, 33196781). When bound by ligand, ALK activates several downstream signaling pathways including the JAK-STAT, RAS-MAPK, and PI3K-mTOR pathways (PMID: 27573755). Translocations of the *ALK* gene leading to constitutive activation are common in cancer and define a subset of non-small cell lung cancers (PMID: 27573755).*ALK* fusions involving various gene partners have been identified in a number of malignancies including anaplastic large cell lymphoma and inflammatory myofibroblastic tumor (PMID: 29279550, 25723109). Germline gain-of-function mutations in *ALK* predispose carriers to neuroblastoma, and account for 75% of familial neuroblastoma cases (PMID: 33194750).  *ALK* alterations have been identified most prominently in skin, liver, and prostate cancers with a lower incidence in other cancers, and a majority are missense substitutions (cBioPortal, COSMIC).  **ALK Outcomes & Frequencies:**  Somatic alterations in *ALK* include gene fusion, amplification, and ALK point mutations, and are detected in approximately 3.3% of all cancers, with a higher frequency in anaplastic large cell lymphoma, and cancers of the skin, endometrium, lung (specifically non-small cell), and colorectum, among others (cBioPortal, COSMIC, My Cancer Genome, PMID: 29488330, 32664698, 25415690, 29488330)).  *ALK* gene fusions define a particular molecular subtype, and are the most common gene alterations in non-small cell lung cancer (NSCLC), having been identified in 3–7% of NSCLC cases (PMID: 27573755, 27386342, 29488330, 32664698).  A large proportion (90-95%) of *ALK* gene fusions in NSCLC (so-called ALK-positive NSCLC) involve *ALK* and the partner gene *EML4* (PMID: 19667264, 23277484, 29363116, 34589917).  In addition, unproductive *ALK* gene amplification and *ALK* gene copy number gains have been noted in 2.9% and 2.4% of NSCLC patients, respectively (PMID: 32664698).  The various acquired ALK point mutations identified in NSCLC patients have been detected mainly after targeted therapy with ALK tyrosine kinase inhibitors (PMID: 21596819, 21847362, 27432227, 30006516). Germline activating *ALK* point mutations have been linked with disruption of central nervous system development, and mutations including p.R1275Q in the ALK kinase domain are associated with a predisposition to neuroblastoma (PMID: 21972109, 28674118).   **ROS1 Gene Summary:**  *ROS1* (ROS proto-oncogene 1) encodes a receptor tyrosine kinase. However, very little is currently known about the normal function of wild-type (WT) ROS1 in humans (PMID: 23719267). *ROS1* is best known for its role as a genetic rearrangement in several tumor types, especially non-small cell lung carcinoma (NSCLC) (PMID: 22327623). The resultant fusion protein is thought to drive cellular proliferation through a constitutively active ROS1 kinase domain (PMID: 23719267). Primary mutations in *ROS1* however are rare, though secondary acquired point mutations in ROS1 kinase have been reported as a mechanism of resistance in tumors harboring a *ROS1* rearrangement after treatment with targeted therapies (PMID: 25351743).  **ROS1 Outcomes & Frequencies:**  *ROS1* fusions with partner genes *CD74*, *SLC34A2*, *SDC4*, *ERZ*, *TPM3* and others occur in about 1-2% of patients with  NSCLC, subtype lung adenocarcinoma and typically these patients are  young, female, and possess minimal or no previous history of smoking (PMID: 28881815, 25264305, 23788756, Ou S-HI and Nagasaka M. A Catalog of 5’ Fusion Partners in ROS1-Positive NSCLC Circa 2020. JTO Clin Res Rep 1:100048). Targeted therapy with ROS1 tyrosine kinase inhibitors (TKIs) provides deep and durable tumor responses (PMID: 32802958). |

**Methods and Limitations**

**METHODOLOGY**

The individual’s DNA was extracted and fragmented, with fragments from the coding regions of the select gene panel targeted for amplification and sequencing. Reads from the sequence output were aligned to the human reference genome (GRCh37) using the Burrows-Wheeler Aligner (BWA). Variants to the reference were called using the Genomic Analysis Tool Kit (GATK). The variants were annotated and filtered using the Golden Helix VarSeq analysis workflow implementing the ACMG guidelines for interpretation of sequence variants. This includes comparison against the gnomAD population catalog of variants in 123,136 exomes, the 1000 Genomes Project Consortium’s publication of 2,500 genomes, the NCBI ClinVar database of clinical assertions on variant’s pathogenicity and multiple lines of computational evidence on conservation and functional impact. This test has not been cleared or approved by the U.S. Food and Drug Administration (FDA). The FDA has determined that such clearance or approval is not necessary.

**VARIANT ASSESSMENT PROCESS**

The following databases and algorithms are used to annotate and evaluate the impact of the variant in the context of human disease: 1000 genomes, gnomAD, ClinVar, OMIM, dbSNP, NCIB RefSeq Genes, ExAC Gene Constraints, VS-SIFT, VS-PolyPhen2, PhyloP, GERP++, GeneSplicer, MaxEntScan, NNSplice, PWM Splice Predictor. Analysis was reported using HGVS nomenclature ([www.hgvs.org/mutnomen](http://www.hgvs.org/mutnomen)) as implemented by the VarSeq transcript annotation algorithm. The reported transcript matches that used most frequently by the clinical labs submitting to ClinVar.

**LIMITATIONS**

It should be noted that this test is restricted to a limited number of genes and does not include all intronic and non-coding regions. This report only includes variants that meet a level of evidence threshold for cause or contribute to disease. Certain classes of genomic variants are also not covered using the NGS testing technology, including triplet repeat expansions, copy number alterations, translocations, gene fusions, or other complex structural rearrangements. More evidence for disease association of genes and causal pathogenic variants are discovered every year, and it is recommended that genetic variants are re-interpreted with updated software and annotations periodically.

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